Assessing the burden of missing tuberculosis cases in Pakistan

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Dissertation for the degree of philosophiae doctor (PhD)

at the University of Bergen

2015

Dissertation date: 16th October

Year: 2015

Title: Assessing the burden of missing tuberculosis cases in Pakistan

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Print: AIT OSLO AS / University of Bergen

Scientific environment

Centre for international health, University of Bergen

National Tuberculosis Program, Pakistan

SORT IT, The international Union against Tuberculosis and Lung disease, Paris

SORT IT, Medicines sans Frontier, Luxembourg

National TB Control Program

SORT IT
Improving health systems through research

World Health Organization

TDR For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO

MEDECINS SANS FRONTIERES

LuxOR
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International Union Against Tuberculosis and Lung Disease

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Acknowledgements

I have countless thanks to many valuable people who prayed, guided me and encouraged me to achieve this challenging task. First of all, I am grateful to God, the Almighty for blessing me with courage to complete this task. I want to dedicate my PhD Work to my Late Mother the Iron Lady Mrs. SafiaKhatoon, she died on 31st July 2011 during process of my selection in University of Bergen and had a great desire for me to complete my highest level of Education, all the academic excellence I achieved is because of her Prayers with me. May God rest her soul in heaven.

I want to thank the University of Bergen especially my main Supervisor, Professor Sven Gudmund Hinderaker who was very kind to me with greatest support and encouragement to excel in my study progress and publications always available for my queries even on weekends .I want to thank Norwegian government for the financial support through the State Education Loan Fund and to the University of Bergen, Centre for International Health for providing me the opportunity to complete my education.

I am highly grateful to Dr Donald Enarson who was part of my all publications and it was a great honor for me to learn a lot from his guidance right from 2011 from operational Research Course in Paris till date and his support and encouragement was a great source of appreciation for me.

I am very thankful to Dr Ejaz Qadeer who is now my dear husband who encouraged me to do my PhD and supported me all the way from inception of idea, application for selection, progress in research work till completion and allowed me full time concentration on my PhD Work.

I am highly grateful to my dearest supervisor, friend and my mentor late DrAmalBassili who died in August 2014 and she was part of all my publication. She was the one who made me a Researcher actually and transferred all her expertise for Inventory study to me and wanted me to take a lead in facilitating other countries her

wish came true and now I am an international facilitator for Inventory studies across the world.

I am highly impressed and thankful to all my research team both in my office and in field who completed the entire task given to them with full commitment and dedication. The support from National and Provincial Tuberculosis Program is worth mentioned since they provided complete support for the field work for all research studies.

It is worth mentioning to thank ASD the association of social Development for supporting me to apply in UIB as quota student and opened up this great opportunity for me.

I would like to say special thanks to Anna Cordova, Ingvild Hope, SolfridVikøren, UnniKvernhusvik and all the staff at Centre for International Health, for facilitating my work. My special thanks to my class mates and my close friends for their good wishes.

Thanks again finally to my family my husband, my brother and my Father for their unending supports and prayers for my success.

Abstract

Approximately 3 million people get tuberculosis (TB) every year in the Eastern Mediterranean Region (EMRO) of World Health Organization (WHO) and a third does not get TB services. WHO urges countries to find, treat and cure the “missing” 1 million to accelerate progress towards zero TB deaths, infections, suffering and stigma.Pakistan has adopted WHO targets for TB control to achieve case detection rate of at least 70%. Pakistan reported a case detection rate of 58% for all types of TB, and ranks 3rd in ten countries that account for 74% (2.4 million) of the estimated missing cases globally in 2013.

Private sector in Pakistan is huge and caters for an unknown but substantial number of TB patients. These health providers are not obliged by law to notify their TB cases, but some linked to National TB Control Program (NTP) are instructed to notify. This thesis assessed the burden of missing TB cases from national surveillance systems at various levels in health systems of Pakistan.

To assess the extent of missing TB cases from national notifications, an inventory study was conducted in 12 randomly selected districts across Pakistan. The finding implied that the proportion of cases notified to NTP was only 32%, and our estimated incidence rates were significantly higher than 2011 WHO estimates. The same dataset was used to assess investigation and management practices of patients with presumptive TB by private providers. The results revealed that private providers mainly rely on public health sector for diagnosis and majority use both CXR and smear microscopy for diagnosis which revealed a great potential to engage them.

A cohort study was done to assess proportion of lost patients with presumptive TB before diagnosis. This intervention significantly reduced proportion of those lost with presumptive TB .The study provides evidence that loss to follow up can be significantly improved by strategies such as encircling presumptive TB cases and simple comparison of registers. In another record review the loss of confirmed TB cases after diagnosis was estimated by comparing the laboratory registers with

treatment registers. The loss was significantly higher in tertiary care hospitals compared to rural health centers.

To identify TB cases missed by routine surveillance in hard to reach areas such as slums, chest camps were arranged and engaged private providers in order to increase TB case detection. This strategy can significantly increase the number of smear-positive TB case notifications.

List of publications

I. Fatima R, Harris RJ, Enarson DA, Hinderaker SG, Qadeer E, Ali K, Bassili A. Estimating tuberculosis burden and case detection in Pakistan. Int J Tuberc Lung Dis. 2014; 18(1):55-60.

II. Fatima R, Qadeer E, Enarson DA, Hinderaker SG, Harris RJ, Yaqoob A, Bassili A. Investigation of presumptive tuberculosis cases by private health providers: lessons learnt from a survey in Pakistan. Public Health Action. 2014; 4(2):110-112.

III. Fatima R, Qadeer E, Hinderaker SG, YaqoobA, Enarson DA, Bassili A, ul Haq M, Javed B. Can the number of patients with presumptive tuberculosis lost in general health services in Pakistan be reduced? Int J Tuberc Lung Dis. 2015; 19(6):654-656.

IV. Fatima R, Qadeer E, Enarson DA, Bissell K. Comprehensiveness of primary services in the care of infectious tuberculosis patients in Rawalpindi, Pakistan. Public Health Action. 2011, 1(1):13-15.

V. Fatima R, Qadeer E, Enarson DA, Creswell J, Stevens R, Hinderaker SG, ul Haq M. Success of active tuberculosis case detection among high-risk groups in urban slums in Pakistan. Int J Tuberc Lung Dis. 2014; 18(9):1099-1104.

List of Abbreviations:

ACF	Active Case Finding
BHU	Basic Health Unit
BMU	Basic Medical Unit
CI	Confidence Interval
CXR	Chest X-Ray
DHQ	District Head Quarter
DOTS	Directly Observed Treatment Short-Course
DTC	District TB Coordinator
EMRO	Eastern Mediterranean Regional Office
FO	Field Officer
HBC	High Burden Country
HIV	Human Immunodeficiency Virus
LED-FM	Light-emitting diode (LED) fluorescence microscopy
MO	Medical Officer
NPO	National Program Officer
NTP	National Tuberculosis Program
PHC	Primary Health Care
PPM	Public-Private Mix
PTP	Provincial TB Control Program
RHC	Rural Health Centre
TB	Tuberculosis
THQ	Tertiary Head Quarter
WHO	World Health Organization

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1. Introduction

1.1 Overview of Tuberculosis

Tuberculosis (TB) is a chronic infectious disease mainly caused by *Mycobacterium tuberculosis*. It is an airborne disease; its transmission begins with a human source most often a person with active pulmonary TB. When such an infectious patient coughs, sneezes or talks, aerosols are formed in lungs and expelled. These aerosols contain micro-particles that carry the bacilli and can be inhaled by others. The disease affects lungs in approximately two thirds of cases but almost all other organs can be infected. Infected people develop TB mostly within five years after TB infection but it can also happen at any point later in life, sometimes many years after infection (1–3).

To understand the epidemiology of TB a model was derived from the TB classification of the American Thoracic society and the United States Centers for Disease Control (now Centers for Disease Control and Prevention), shown in figure 1 (4,5). According to this model, four distinct steps in the pathogenesis of TB can be identified: exposure, infection, disease and death.

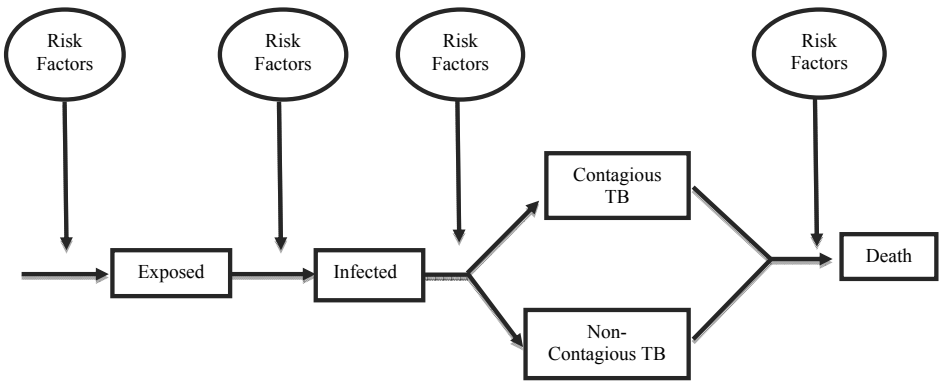


Figure 1: Model for TB epidemiology: following the pathogenesis of TB.

Source: Rieder (1995) Infection 23(1):5-8

Risk of exposure to TB: The major factors that determine the risk of becoming exposed to tubercle bacilli include the number of new infectious cases in the community, the duration of infectiousness and the number and nature of interactions between a case and a susceptible contact. Number of case-contact interactions depends upon population density, family size, difference in climatic conditions, age of sources of infection, and gender can be a risk factor to develop TB (3). Also, culture determines how people interact and hence have an important role to play in exposure to the bacteria.

Risk of acquiring TB infection: The risk of subclinical infection depends on the number of infectious droplet nuclei per volume of air and the duration of exposure of a susceptible individual to that particle density (3).

Risk factors associated with TB disease: Many risk factors for TB disease are exogenous and determined by characteristics of the source case, the environment and duration of exposure. The endogenous risk of developing TB is determined by the integrity of cellular immune system (3).

Risk of death from TB: Sputum smear-positive pulmonary TB has a much higher case fatality than sputum smear-negative TB, reflecting much higher bacterial load. The risk of death from TB is dependent on the site, type and severity of disease, and timeliness of diagnosis. Given that most deaths from TB are preventable; the death rate from TB is still unacceptably high. In 2013, 9.0 million new TB cases and 1.5 million TB deaths (1.1 million among HIV -negative people and 0.4 million among HIV-positive people) were reported (6). TB is top third cause of death in Pakistan and approximately 5% of all deaths occurred due to TB (7).

1.2 Major Risk Factors associated with Tuberculosis

Some major risk factors of TB are listed below

1.2.1 Age

The risk of acquiring TB infection increases with age, probably because of increasing number and frequency of contacts. Globally, the greatest TB incidence and mortality is found in 15-49 years age group (8–10) whereas as in Europe TB is more prevalent in older. In 2013, globally half a million children of age between 0-14 years were infected with TB and of them 80,000 died from TB (6). As burden falls, there is less new infection and hence fewer children are infected, whereas cases due to reactivation of latent TB infection will still continue to appear at later ages.

1.2.2 Gender

The degree of social interactions differs by gender in different societies. Studies show that men often account for a higher proportion of notified TB cases than women (11,12), varying from 0.5 in Afghanistan to 3.0 in Viet Nam and 1.0 in Pakistan (6,13). Variation among countries may reflect real differences in epidemiology as well as differential access to or use of health care services linked to national TB control program (NTP) (6). For example, compared with men, women in Bangladesh experienced longer delays at various stages of the health seeking for TB (14).

1.2.3 Socio- Economic Status

Studies provide evidence that the TB case rate in urban areas is higher than the rural areas, probably because of higher population density and higher tendency of immigration (15). This low TB notification rate in rural areas was explained by limited access to health services, poor health seeking behavior and deficient knowledge regarding TB (16–18). Poverty and overcrowding has the potential to increase exposure of susceptible individuals to infectious TB cases (19).

1.2.4 Environmental Factors

Environmental factors related to the risk of infection and development of TB after infection include genetic susceptibility, ethnic group, malnutrition, human immunodeficiency virus (HIV) infection, migration, population density, climate, alcoholism, smoking and urbanization (20,21). Environmental factors may have an

impact on the incidence of TB as these factors effect on both the risk of infection and the risk of disease once a person is infected.

1.2.5 Other Risk Factors

Various studies reported history of asthma, family history of TB, single marital status, low education level, indoor air pollution and use of immunosuppressive drugs as important factors to develop TB(5,22,23).Although exposure to infection is a risk factor in the etiology of TB, variability in individual susceptibility or resistance may depend on genetic constitution. Genetic factors that may affect the risk of TB include gender, body build, HLA types, blood groups, hemophilia. (10,24–26). TB is more common among the population who already suffer from silicosis, diabetes mellitus, malignancies, renal failure, measles, gastrectomy and jejunoileal bypass (27–33). According to the World Health Organization (WHO), over 95% of TB deaths occur in low and middle-income countries and above 90% of cases occur in these countries (34).

1.3 Social Impact of TB

The stigma attached with TB has many social implications. Due to the air borne transmission of TB, close interaction with infected individuals is often avoided. Thus, the quality of life becomes significantly lower in infected individuals as compared to those not infected (35). In Urban areas, majority of the population are aware of prevailing health care system for treatment of TB (36). TB is the third-leading cause of death for women aged 15 to 44. This is of particular social importance because these are the prime years for women to bear children.

1.4 Economic Impact of TB

It is evident that the world's poorest countries have the highest incidence of TB, and due to TB these countries are bearing a loss of an estimated $1 to $3 trillion in a decade (37). This becomes even more detrimental when we review the nature of the

disease and find that it is more prevalent in people in their most productive years between ages of 15 and 44. The World Bank estimates that due to TB some countries faced a decrease of their gross domestic product (GDP) in the range of 4-7% (38).

In addition to country level cost, there are indirect costs to individuals, including travel expenses, medicine, consultation fees, missed days of work and any other preventative measures. The major indirect cost of TB is income lost due to missed days of work, resulting in average lost potential earnings of 20% to 30% of annual household income. For the families of those who die from TB there is also an average loss of about 15 years of income because of premature death (38).

1.5 The Global Burden of TB

TB is a contagious disease affecting millions of people worldwide and if treated properly is curable. Until the mid-20th century, it remained a leading cause of death in the developed world and still a public health problem in many developing countries. It is estimated that currently about one third of the worldwide population is infected with TB and 5-10% of these infected individuals will be more prone to have TB at some point in their lives (39). If smear-positive TB patients are left untreated, about two thirds of them will die within 8 years (40). Even in patients on TB treatment, the case-fatality rate can exceed 10% with high HIV rates, high levels of drug resistance and poor treatment adherence rates (41).

Globally, the impact targets are “to halt and begin to reverse the incidence of TB by 2015 and to reduce by 50% prevalence and mortality rates by 2015, relative to the 1990 levels”. The outcome targets i.e. “to achieve a case detection rate of at least 70% for new SS+ cases and to reach a treatment success rate of at least 85% for such cases” were first established by the World Health Assembly (WHA) in 1991. Within the millennium development goal’s framework, these indicators are defined as the proportion of cases detected and cured under Directly Observed Treatment Short-Course (DOTS). Recently post 2015 strategy is launched by stop TB partnership

which aims to end the global TB epidemic, the targets are to reduce TB deaths by 95% and to bring down new cases by 90% between 2015 and 2035(42).

Despite efforts to control and treat TB, in 2013 an estimated 9.0 million people developed TB and 1.5 million died from the disease, 360 000 of whom were HIV-positive. These deaths included 0.5 million among women, making TB one of the top killers of women worldwide. There were 80 000 deaths from TB among HIV-negative children in the same year (6).

1.6 The burden of TB in Pakistan

In Pakistan the life years lost, by causes, is mainly due to communicable diseases (55%) followed by non-communicable disease (32%) and injuries (13%) (43). Pakistan ranks 4th among the 22 TB HBCs and 4th among 27 multidrug resistance HBCs in the world. Pakistan contributes about 61% of TB burden in the Eastern Mediterranean Regional Office (EMRO) region. According to WHO report 2014, the incidence of TB cases (all types) in Pakistan is 275/100000 population per year or around 500000 TB cases per year. The prevalence of the disease is estimated at 342/100000 population or approximately 620000 cases. In 2013, 298446 TB cases (all ages, all forms) and 111682 bacteriological confirmed cases were notified in Pakistan (6).

NTP Pakistan has a stewardship role in TB control efforts in the country. NTP is fighting against TB in the country with the support of the Provincial TB Control Programs (PTPs). NTP is a vertical program integrated into primary health care (PHC). The program is responsible for overall management of the TB control activities in the country. The NTP has various categories of managerial, technical and administrative staff working at the national and provincial levels. The delivery and management of TB care is integrated within district healthcare services so that health care can be provided close to the patient's home. There is 100% DOTS coverage in engaging public health facilities such as basic management units (BMUs) including basic health units (BHUs), rural health centers (RHCs), district head quarters

(DHQs), and Tertiary care hospitals. Since 2001, more than 1.5 million TB patients have been provided free of cost diagnostic/treatment facilities in Pakistan through 1500 diagnostic centers and more than 4000 treatment centers operating under the NTP Pakistan. But still there is Non-NTP public sector uncovered which mainly includes hospitals and health care centers being managed by organizations such as the Pakistan Armed Forces, Social Security and Fauji Foundation. These health facilities are not covered by the NTP and have an enormous potential to contribute to TB care delivery in the country (44).

1.7 The Health System of Pakistan

1.7.1 Public Sector

The health system is generally not strong and services are highly unregulated. Communicable diseases are still the leading cause of morbidity and mortality and non-communicable diseases are on rise. The public sector is main source of provision of preventive care and hospital care to urban and rural populations. In the provision of curative care for minor ailments, the public sector caters services to around 25% of the population. Health services in the public sector are provided by various types of general and specialized hospitals. There is also a network of primary health care outlets including BHUs, RHCs, dispensaries and maternal & child health centers which are mainly under the control of the provincial departments of health. Other semi-public sectors include health care institutions established and run by armed forces, police, railways, Fauji foundation, municipal authorities and social security institution. In each district usually there is one DHQ Hospital, three to four THQ Hospitals, 10 to 15 RHCs and 50 to 100 BHUs. RHC and BHU are first level primary health care facilities and generally deal with uncomplicated cases, in addition to preventive and promotional activities. DHQ and THQ level hospitals are secondary health care level facilities and are involved in the treatment of less complicated cases. There are tertiary level hospitals in provincial capitals and in some large districts which deal with referred and complicated cases.

1.7.2 Private Sector

The private sector is large and unregulated comprised of both qualified and unqualified service providers in the disciplines of Allopathy, Homeopathy and *tibb*(Traditional Herbal Medicine). Private hospitals may provide better services and charge patients for care that range from low to high depending upon the type of private hospitals. Patients with low income usually spend on health between Rs 5000-10000 per month (45). The private sector caters for about 75% of the population's curative primary health care needs in addition to low cost hospital care (46).

Qualified providers include the not-for-profit non-government organizations as well as for-profit private sector institutions and individual practitioners. There are many large private teaching hospitals present in the country that are managing infectious and non-infectious diseases. In 2008, there were more than 200,000 private providers in Pakistan, but only 2000 (less than 1%) were found reporting to NTP (47). These health care providers are encouraged to refer patients to the NTP but as evident in other developing countries, this happens with varying comprehensiveness of notification. In 2013, 18% of the TB notification in Pakistan is contributed by private sector (6) and it is expected that we are missing many TB cases from private sector. PPM is a crucial component to meet WHO and Stop TB Partnership targets for global TB control. In Pakistan, Mercy Corps workswith the public and private sectors to improve case detection, treatment and reporting of TB cases by private providers with a particular focus on private providers and private laboratories. Within the country PPM interventions have achieved some promising initial results but there is a critical need to enhance the degree of collaboration among those currently engaged and reach out to a greater number and range of providers.

1.8 Rationale

Approximately 3 million people get TB every year in the EMRO region and a third do not get the TB services. many of these cases are either never diagnosed or they receive treatment in the private sector (6,48). Untreated patients continue to transmit

TB and those treated incorrectly can develop drug resistance; in both cases mortality is high (49). WHO is urging countries to find, treat and cure the "missing" 1 million cases who do not get proper TB services to accelerate progress towards zero TB deaths, infections, suffering and stigma.

Based on WHO estimates, Pakistan reported a case detection rate of 58% for all types of TB, and is listed among one of the countries that are not on track to reach any of the three targets of reductions in TB burden because of several challenges, including resource constraints, conflict and instability. Pakistan ranks 3rd in ten countries that account for 74% (2.4 million) of estimated missed cases globally.

Outside NTP, private and public providers manage an unknown but probably substantial number of TB patients. These health providers are encouraged to refer patients to the NTP but as in other developing countries, this happens with varying comprehensiveness of notification (50). PPM approach is a crucial component to meet WHO and Stop TB Partnership targets for global TB control (51). Lack of involvement of all health care providers that may contribute to under-reporting, delays in diagnosis, inappropriate and incomplete treatment and increasing drug resistance puts unnecessary financial burden on patients (52–54).

TB incidence is difficult to measure at national level with limitation of cost, time and feasibility (53). Notifications of TB cases provide a good proxy indication of TB incidence in countries that have both high-performance surveillance systems and complete access to quality health care. But where these criteria are not met, estimates of TB incidence can be obtained from an inventory study (55–58). In 2013, 18% of the notification was contributed by private sector in Pakistan (6) and it is expected that we are missing many cases from private sectors since NTP has a very limited (less than 1 percent) coverage of private providers (47). Thus, the first research question was: what is the actual burden of TB and the level of under-reporting from non NTP Providers in Pakistan?

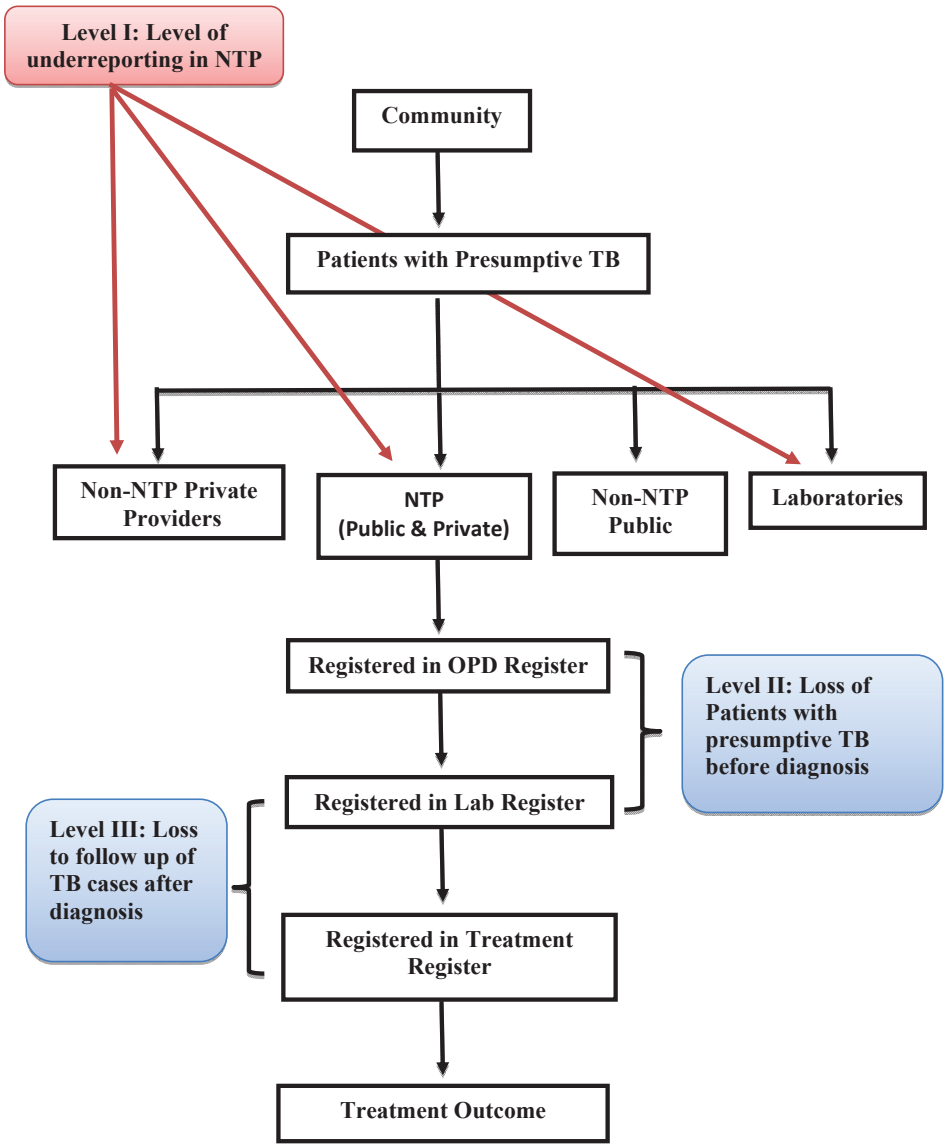
Lack of community involvement and limited engagement of private sector are still challenges for the program (59). The first point of contact is with the private sector in 75% of cases (46). Involvement of private providers through the PPM initiative may accelerate the case findings in the country since majority of unreported cases are with private sector (46,51). The exact management of TB by private providers is unknown because of limited knowledge available. Based on this the second research question was: how do doctors in private sector diagnose and manage TB patients?

The patients with presumptive TB are either referred to public health sector (NTP laboratories) or private laboratories for diagnostic process i.e. sputum smear microscopy and CXR examination, and not all of them are notified to NTP (52,60,61). This may result in increased risk of morbidity and mortality of TB in the community from increased transmission of TB (62). The presumptive TB cases (previously called suspects) management is a challenge for the program and there is need to minimize loss of patients with presumptive TB who seek care at outdoor department of public hospitals and majority are lost in the system before registration. The third research question was: what proportion of presumptive TB patients is lost before diagnosis?

TB treatment, prevention and control depend on ensuring that all diagnosed infectious patient's timely initiate and complete treatment. According to NTP guidelines, every confirmed TB case from laboratory must initiate treatment and registered in patient register. But some TB cases may be identified in laboratory and never initiate treatment (63–65). Patients who are not enrolled on treatment, specially smear positive cases, are a challenge in health system in various ways if they are not promptly recorded they may be difficult to trace and become a source of infection in community and may lead to false estimates of treatment success (66). In Pakistan, tertiary care hospitals have recently been engaged to provide TB services, and these hospitals face a huge workload with human resource constraints. Thus, the fourth research question was: how many patients diagnosed with TB are lost before they start their treatment in tertiary care hospital and peripheral diagnostic centres?

Early identification of sputum smear-positive cases with rapid initiation of TB treatment are keys to control TB (55) and are part of the DOTS strategy model of passive case-finding that has been adopted by most NTPs (67). Various National prevalence surveys in HBCs have demonstrated that more than half of TB cases remain undetected (68). Although passive case detection has shown a positive impact on case detection in HBCs (69–71). Active case finding (ACF) strategies are employed as a supplementary approach to reduce delay and reach to the cases missed by routine surveillance (72–74). Many ACF initiatives among high risk groups have shown promising results (75–79). Various studies from other parts of world provide evidence of improved case detection through chest camps (80,81). Scaling up of PPM approach is effective to increase case detection by between 10% and 60% and improve treatment outcomes to >85% (82,83).There is high potential for the most neglected hard to reach areas such as slums to contribute more TB cases through strategies like ACF by arranging chest camps and engaging private providers in order to increase TB case detection. The fifth research question was: how many TB cases can be identified by chest camps in slums and involving private providers?
TB cases who remain undetected by NTP or a national surveillance system at various levels in health systems is shown in a conceptual model in Figure 2 below.

Figure 2: Missed undetected TB cases at various levels in health system model



2. Objectives

2.1 Aim

The main goal of this thesis was to assess the burden of missing TB cases in Pakistan.

2.2 Specific Objectives

The specific objectives were to

1. Estimate TB incidence in Pakistan using capture recapture analysis (Paper I: Inventory study)
2. Determine the extent of under reporting of TB cases from all providers not reporting to National TB control in Pakistan (Paper I: Inventory Study)
3. Assess the clinical practices of private providers for investigating patients with presumptive TBin 12 districts of Pakistan. (Paper II: Private investigation practices)
4. Evaluate patients with presumptive TB detected before and after a simple intervention using outpatient register and laboratory register in two districts in Punjab, Pakistan. (Paper III: Loss of patients with presumptive TB)
5. Estimate initial loss to follow up of smear positive cases in tertiary care hospital and peripheral health facilities in Rawalpindi district in Pakistan. (Paper IV: Initial loss to follow-up)
6. Evaluate the additional yield of smear-positive TB by active case finding at community-based chest camps in a high risk population in Sind, Pakistan. (Paper V: Active case finding in slums)

3. Methods

3.1 Settings

Pakistan belongs to the Asian Continent and covers an area of 706096 square kilometers and estimated population is 182.5 million people; approximately 65% of them live in rural setting. Pakistan includes 141 districts located in five provinces Punjab, Sindh, Balochistan, Gilgit-Baltistan and Khyber Pakhtunkhwa, in addition there are three regions (Azad/Jammu/Kashmir, Federally Administered Tribal Areas (FATA) and Islamabad Capital Territory). Nearly half of the population of the country lives in Punjab Province. In 2013, the life expectancy was estimated at 68 years for females and 64 for males. The mortality rate in children under 5 years was 72 deaths per 1000 live births and the maternal mortality ratio was 260 deaths per 100000 live births (84). Pakistan is still in the process of epidemiological transition; analysis of years lost to death or disability indicates that 55% are related to communicable diseases, 32% to non-communicable diseases and 13% to injuries (43). According to the National Health Accounts (2009-10), the annual health expenditures per capita were estimated to be 31 US$, the ratios of health expenditures over GDP (2009-10) were 3.0% while this ratio for public and private sector health expenditures was 9.2% and 2.5%, respectively (47). Pakistan ranks 4th among HBCs and third amongst ten countries that account for 74% (2.4 million) of the estimated “missed” cases globally, 2013 (6). Some health indicators of Pakistan are given in table 1.

TheNational TB Control Program (NTP)

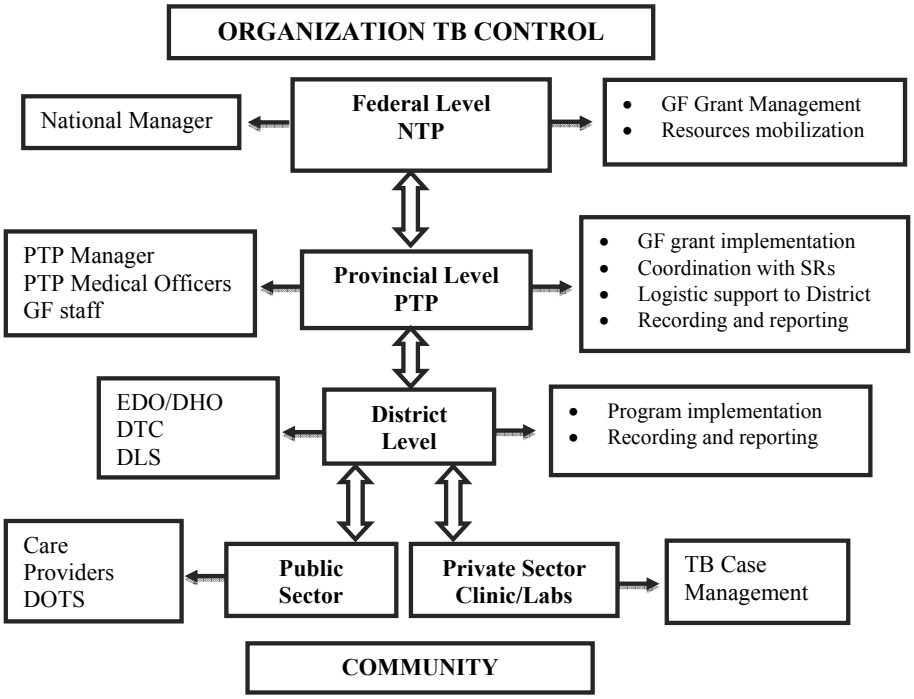
NTP is a department of the Ministry of Health, Government of Pakistan. NTP is a Vertical program integrated into PHC. It has been working since 2000 and is responsible for nationwide control of TB. The main responsibilities of NTP include

policy formulation and strategic planning, technical support to provinces, supervision, monitoring and evaluation, research and development.

The clinical and practical case management is done by various facilities and is monitored and supported by NTP. The Program is currently implementing several projects and interventions in coordination with provincial, district and other implementing (non-governmental) partners on various TB control interventions in NTP linked facilities.

While there are facilities that are not linked to NTP known as non-NTP public and private facilities and non-NTP laboratories. The organizational structure of NTP is given in figure 3.

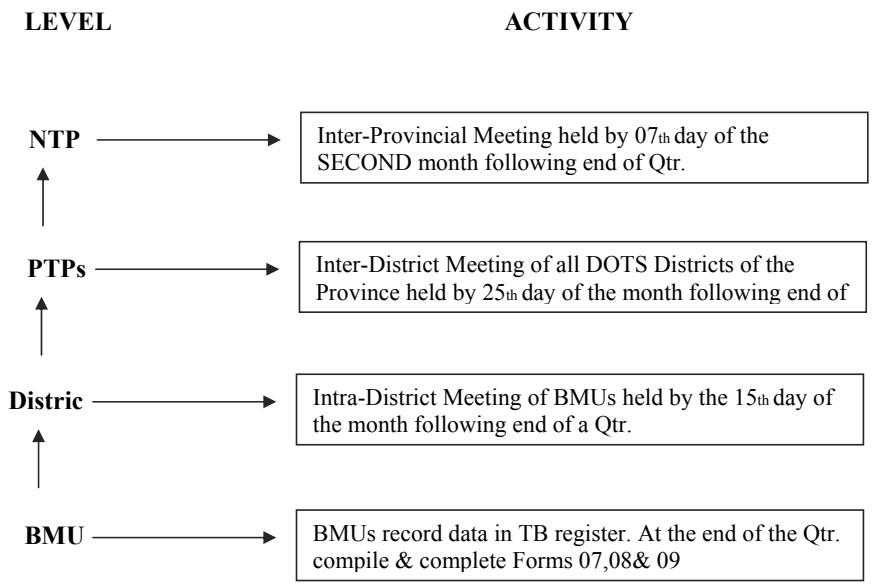
Figure 3: Organizational structure



Abbreviations: BMU/TC= Basic Medical Unit/TB Centers, DHO = District Health Officer, DLS = District Laboratory Supervisor, EDO = Executive District Officer, GF=Global Funds, NTP=National TB Control Program, PTP=Provincial TB Control Program, SR=Sub-recipient.

TB services are integrated into the primary health care system at district level and are delivered by chest clinics in tertiary (public and private), district and sub district hospitals, RHCs and BHUs. There is efficient vertical reporting, monitoring and supervision system in place which is the backbone to maintain quality of TB services in the country. There are regular surveillance meetings at national, provincial and district levels. Data is generated at BMU level, at the end of every quarter there is a data transfer at district level in intra-district meeting and then subsequently to provinces in inter district meeting and finally to NTP in interprovincial meetings . Details of flow of data process are given in Figure 4.

Figure 4: Flow of data in National TB Control Program



In the inventory study, capture recapture analysis was done to estimate under - reporting in 12 districts across Pakistan by engaging all TB care providers not linked to NTP such as non-NTP (public, private and laboratories). The following districts were selected from the main four provinces:

1. Lasbella 2. Mirpurkhas 3.Rawalpindi 4.Khushab 5.Lodhran 6.Zhob 7.Washuk

8. Rajanpur 9. Larkana 10.Buner 11.Battgram 12. Swat.

Map of the selected districts is attached in annex I.

Punjab is the 2nd largest and most populous province of Pakistan. It covers 205345 km2 (23.3% of the national area) and has a population of about 73.6 million (53.7% of the national population). It has 5 divisions, 22 districts and 81 Tehsils and 62.6% of its population live in rural areas (85). On average 60% of TB cases (for both any form and smear-positive TB) are notified from Punjab (86). The routine practice is towrite into the general outpatient registers all patients seeking health care to respective health facility. The management of patients with presumptive TB relies on further investigations. A separate suspect register to record patients with presumptive TB was recommended (87,88) but not in use in Pakistan, mostly because of overburdened staff in public health facilities. In paper III (Loss of presumptive TB cases), public health facilities in the districts of Faisalabad and Chakwal were selected. In paper IV (Initial loss to follow up), all public health facilities in Rawalpindi city (4.5 million inhabitants) were included in the study.

In paper V (Active case finding in slums), the study was done in Sindh province with population of 40 million inhabitants (2nd populous province) in an area of 141102 km^2. It is divided into 23 districts. All districts have urban slums with highest concentration in the largest city Karachi. The health infrastructure is not developed in these slums and access to primary health care services is poor. TB services are integrated into primary health care system at district level and are delivered by chest clinics in tertiary (public and private), district and sub-district hospitals, RHCs and BHUs. On average 20% of TB cases are notified in Sindh (86). It is expected that there are many TB cases missed in slums since NTP do not have coverage in these areas. Health care is provided by both qualified and unqualified medical professionals. According to Pakistan Medical and Dental Association, total number of registered private providers in 2014 was 57110 in Sindh (89). A study was conducted in slums of districts (Dadu, Thatta, Larkana and Sanghar) and five towns (Jamshed, Gadap, Orangi, Baldia and Kemari) of Karachi district to evaluate additional yield of smear-positive TB by active case finding at community-based chest camps and

involving private providers. The estimated 2011 mid-year population of Karachi, Larkana, Dadu, Sanghar and Thatta was 2 993 800, 502 607, 687 307, 1 158 856 and 702 535, respectively. Map of selected districts in paper V (Active case finding in slums) is attached in annex IV.

Table 1: Health Indicators of Pakistan for 2013*

Indicators	Rate (1000000 population)
Population	182.5 million
Incidence of TB all form per 100000	275 (205-357)
Prevalence of TB per 100000	342 (284-406)
Case detection rate	58%
treatment success rate of new cases registered in 2012	91%
TB Mortality (excludes HIV+TB)	56 (25-92)
Notified TB cases	298 446
Public Health Facilities**	13002
Private Hospitals	4380
Private Providers	206712

*Source: WHO report 2014(6). ** Public health facilities include Hospital, Dispensaries, Maternal and Child Health Centers, Rural Health Centers, Basic Health Units, TB Centers.

3.2 Study Population

In paper I (Inventory study) & II (TB investigation practices by PP), all TB care providers in the non-NTP sector were involved in inventory study. Patients with symptoms suggestive of TB in 12 selected districts in Pakistan were enrolled and all individuals with a cough of >2 weeks' duration who consulted non-NTP public or private providers for their symptoms from January to March 2012 were included. Districts were stratified according to four levels of smear positive notification rates low notification rate (<25% percentile), intermediate (25-50%), high (50-75%) and very high (>75), 3 districts were selected from each level by randomization. All non-NTP facilities in selected districts were mapped and consenting providers were

enrolled. Patients with presumptive TB were consecutively enrolled and followed up until confirmation of diagnosis. Following a pilot study to assess feasibility (90) data for record linkage were collected from July 2011 to June 2012 and data from modified suspect and laboratory registers was collected from Jan to Mar 2012. The same data set was used for Paper II (Private investigation practices).

In paper III (Loss of patients with presumptive TB), all patients with presumptive TB identified and entered into outpatient registers who fail to be registered in a laboratory register for any reason were listed to assess loss of symptomatics in Chakwal and Faisalabad from Jan -Dec, 2013. Faisalabad district (population 7.4 million) and Chakwal (population 1.4 million) were selected as intervention while Okara (population 3.1 million) and Khushab (population 1.2 million) were selected as control areas based on similarity with respect to population, number of diagnostic centres and demographic indicators to intervention districts.

In paper IV (Initial loss to follow up), all registered smear-positive patients in Rawalpindi district (population 4.5 million) during 2009 in laboratory register who were found missing in treatment registers were recorded to assess the burden of initial loss to follow-up .

In paper V (Active case finding in slums), the study population included all patients with presumptive TB attending chest camps and presenting to clinics of private providers in selected slums of Sind province.

3.3 Study Design

In the inventory study, the study design was cross-sectional. Simple random sampling was used in which large self-contained geographical areas were selected followed by prospective collection of data of TB cases diagnosed by all health-care providers within these areas for a specified time period. A prospective longitudinal surveillance system for identifying TB cases was established among all non NTP Private and public providers in 12 districts (14 million populations) from Jan-March 2012.

In paper III (Loss of patients with presumptive TB) a cohort study was conducted comparing patients with presumptive TB not identified in register before and after an intervention period from Jan-Dec, 2013 to assess loss of TB symptomatics. A simple strategy was introduced by using exit outpatient registers and marking patients with presumptive TB with a red circle and developing a list of patients with presumptive TB who were not initiated on treatment and recorded in the treatment register.

In paper IV (Initial loss to follow up), a cohort study was done based on retrospective record review to assess the initial loss to follow up after diagnosis in 2009 in all TB diagnostic centres of Rawalpindi District including five tertiary care hospitals and 16 RHCs.

In paper V (Active case finding in slums) quasi-experimental design was used to assess the TB case notification before and after an integrated intervention i.e. chest champs and involving private providers.

3.4 Research Framework

To achieve the targets of reduced mortality and morbidity from TB, measures for early identification of unrecognized TB cases to minimize TB burden is important. The aim of this thesis is to assess the burden of missing TB cases in Pakistan. These studies are focused to measure level of under reporting, estimate loss of symptomatics, initial loss to follow up and propose an innovative approach of ACF with involvement of private providers to reach the unreached. These studies were focused at various levels in health system model as shown in Figure 5.

Figure 5: Theoretical Framework

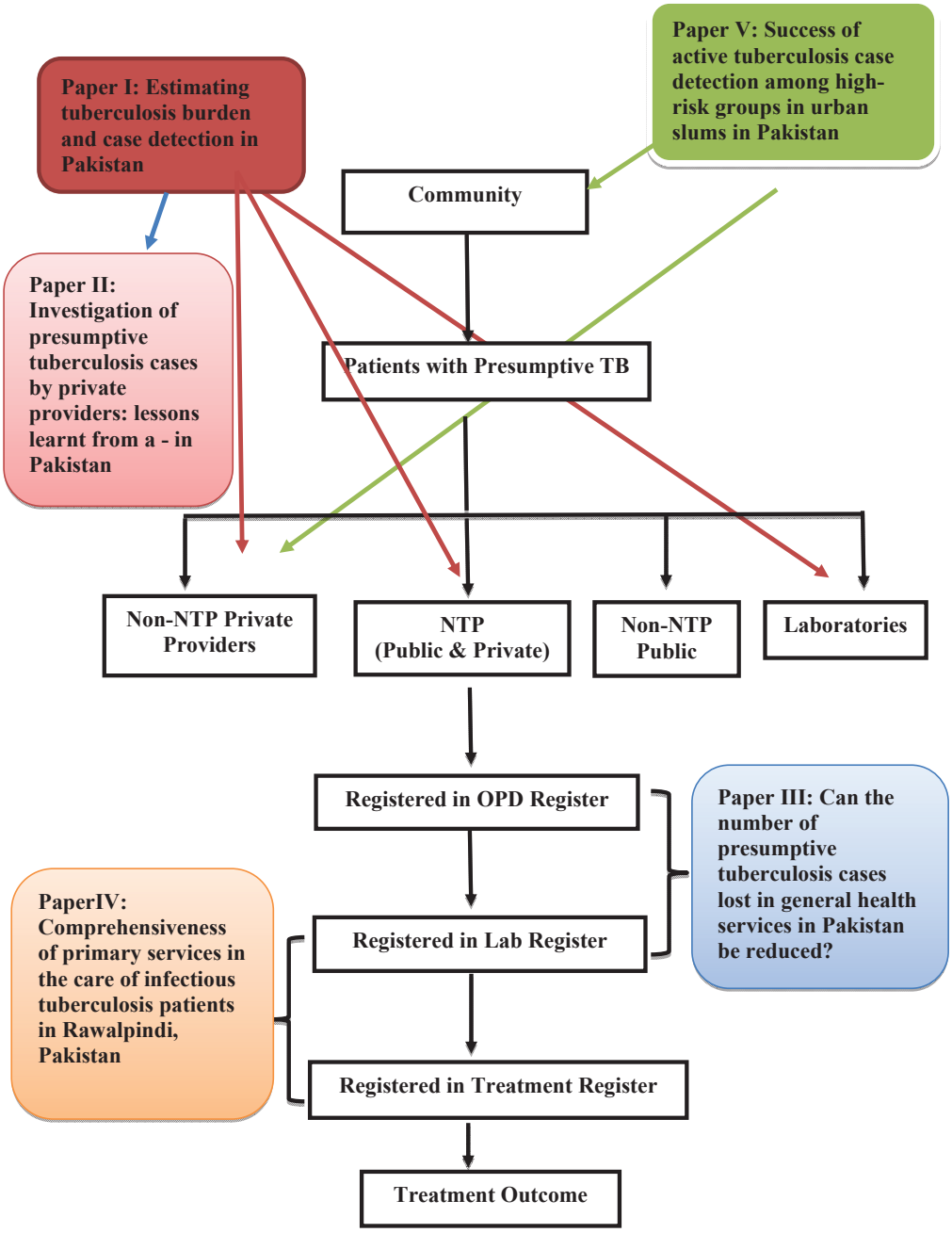


Table 2: Summary of studies conducted: design, population and study period

Paper	Titles	Study Designs	Study Population	Study Period
I.	Estimating tuberculosis burden and case detection in Pakistan	Cross sectional	Diagnosed TB patients in all sources including NTP and non-NTP	Jan – Mar, 2012
II.	Investigation of presumptive tuberculosis cases by private providers: lessons learnt from a survey in Pakistan	Cross sectional	Presumptive TB cases identified by private providers	Jan – Mar, 2012
III.	Can the number of presumptive tuberculosis cases lost in general health services in Pakistan be reduced?	Cohort	Missing patients with presumptive TB in lab registers	Jan – Dec, 2013
IV.	Comprehensiveness of primary services in the care of infectious tuberculosis patients in Rawalpindi, Pakistan	Cohort	Smear positive TB cases	2009
V.	Success of active tuberculosis case detection among high-risk groups in urban slums in Pakistan	Quasi experimental before-and-after	Patients with presumptive TB attending chest camps and private providers in Sindh province	Apr 2011 - Sep 2012

3.5 Definition of Terms

Some important terms are defined below:

- **Active Case Finding:** implies TB-investigations of groups of symptomatics who have not sought help, as opposed to those who seek health care on their own initiative.
- **Case Ascertainment Rate:** Number of observed cases divided by the estimated total number of cases.
- **Estimated Case Detection Rate:**The estimated case-detection rate (CDR) is defined as the number of TB cases notified to NTP divided by estimated number of TB cases.
- **Incident TB Cases:** Estimated number of new TB cases arising in a given time period.
- **Initial Loss to Follow-Up:** are those smear positive patients found in laboratory register who could not be identified in treatment registers.
- **Inventory Study:** An inventory study is a study of level of under-reporting of existing TB cases and compares number of cases meeting standard case definitions recorded in all or a sample of public and private health facilities with the records of cases notified.
- **Notified TB Cases Inventory Study:** refer to all TB patients registered with NTP between 1 January - 31 March 2012 and all TB cases confirmed by non-NTP providers according to NTP criteria during same time period.
- **Passive Case Finding:** Passive case finding means identifying TB cases when they come to a clinic or health facility to get relief for their TB symptoms.
- **Patient Diagnostic Rate:** The PDR is calculated as the number of newly-reported smear positive TB cases per 100000 population per year (notification rate) divided by the prevalence of new cases of smear-positive TB per 100000.
- **Patients with Presumptive TB**: refer to individual with cough > 2 weeks with or without associated symptoms such as fever, weight loss, night sweats (previously known as TB suspects).

- **Private-Public-Mix (PPM):** An international initiative to stimulate and assist collaboration between NTP and the private health sector.
- **Under-Reporting:** refers to the numbers of TB cases confirmed but not notified to NTP

3.6 Study Outcomes

In paper I (Inventory study), the outcomes were the estimated incidence of new TB patients and the estimated level of under-reporting, which is the proportion of TB cases that are not notified to NTP.

In paper II (Private investigation practices), the outcomes were investigation practices of patients with presumptive TB, categorised into investigation, management, referral domains.

In paper III (Loss of patients with presumptive TB), the outcome was the proportions of presumptive TB patients not identified in laboratory register.

In paper IV (Initial loss to follow up), the main outcome was the proportion of initial loss to follow up.

In paper V (Active case finding in slums) the main outcome was the number of TB cases detected from chest camps activities and number of TB cases reported by involved private providers as linked intervention.

3.7 Data Collection Methodology

In the inventory study four sources of information were used: 1) NTP TB Register 2) non-NTP public health facilities 3) private health facilities and 4) private laboratory facilities. NTP's standard recording and reporting formats were used to collect data on all registered TB patients in NTP TB register. Modified OPD and laboratory

registers were developed and provided to all non-NTP health care providers to record management of patients without changing their routine practice. Field officers (FOs) and district TB coordinators (DTCs) were trained on the data collection tool and they visited selected health facilities on weekly basis for record checking for correct entries. They were instructed to evaluate completeness, accuracy and notification status of TB cases. Non registered TB cases were contacted to verify diagnosis per NTP criteria.

In paper III (Loss of patients with presumptive TB) all types of health facilities including BHUs, RHCs, DHQs, THQs and their attached laboratories working under the umbrella of the DOTS strategy and reporting to NTP were included in this study. In intra-district meetings held in intervention districts, medical officers (MOs) were instructed to mark presumptive TB cases in outpatient registers with a red pen. DOTS facilitators were instructed to compare exit outpatient register with laboratory register and make a list of patients with presumptive TB for each facility. Data collectors were trained on data collection tool. Data was collected and verified under supervision of DOTS facilitators and research teams at NTP.

In paper IV (Initial loss to follow up), the study population included all smear-positive TB patients whose residential address was within the district and were listed in the laboratory register at any of the facilities participating in study. All cases recorded as smear positive in laboratory registers were traced in treatment registers. Any patient not found in treatment register was recorded in a data collection tool. All patients on this list were then traced in treatment registers of the other treatment centres in the district, and if found in these treatment registers they were no longer classified as “initial loss to follow-up”.Additional information included age, sex and address (complete address, including street address) to assess distance from health facility.

In paper V (Active case finding in slums), a mapping exercise was performed to identify sites for chest camps based on daily workload, distance from BMU and location in slum. The slum area was divided into clusters with 10 private providers around one laboratory for follow-up microscopy. At least one private provider who

agreed to participate and one paramedic from each of selected clinics were identified and trained on NTP standard training package for private providers. A three days' course by PTP office was conducted to train participating private providers in diagnosis, recording and reporting of TB according to NTP guidelines. In parallel, promotional activities for camps were arranged, such as making announcements through loudspeakers a day before camp, and displaying posters, banners in Urdu & local Sindhi language with information about free general medicines. To attract local community, health fairs were arranged that included street theatre, fun shows and stalls.

One day chest camps were establishment by trained local private providers to refer presumptive TB cases to temporary laboratories in a nearby private provider clinic. Temporary laboratories using light-emitting diode fluorescence microscopy LED-FM equipment were also established. Camps were conducted by five different teams, one in each district, once a week at different sites and a screening questionnaire was used to identify symptoms that required investigation for TB. All screening was performed by local trained private providers. Any person who reported cough of >2 weeks was referred for sputum microscopy. Two sputum samples were collected on same day to avoid any delay in collecting a second sample. All smear microscopy results were communicated to MOs in chest camp. Confirmed TB cases were referred to a private provider clinic situated nearest to their home and were recorded in routine TB registers supplied to the clinic. Treatment was provided by provincial TB control programme and followed by FOs. After the activities of a chest camp were completed, trained private providers were responsible for managing any patients with presumptive TB visiting their clinic. These were registered separately with a record of results in TB registers kept by the same private providers responsible for managing TB cases. The number of chest camps in Karachi was initially 12 per month as an accelerated effort to achieve project target, but was reduced after a year to 6 per month from 1 April to 30 September 2012. Data was collected from two sources 1) from laboratory registers which consisted of numbers of persons attending facility, numbers referred for sputum smear examination and numbers found sputum smear-

positive; and 2) data from treatment registers which comprised information on age, sex, site of clinic and type of TB. Pre-intervention notification rates were collected from routine surveillance data for 18 months before project (1 October 2009–31 March 2011) and for 18-month duration of project (1 April 2011–30 September 2012). FOs was trained before start of data collection.

3.8 Data Validation

In the inventory study, in order avoid duplication in all data sources, a unique identifier was developed based on four names i.e. first name, father name, grandfather name and family name. In case all four names could not be recalled by patient then national ID number was recorded. NTP data of registered patients two quarters before and one quarter after the study period was compared with study data to check and correct any misclassification of patients not diagnosed during study period or referred late for notification. Confirmed non-registered TB cases were added after study period into the NTP register. Monitoring visits were done by FOs and supervised by DTCs to ensure data accuracy. Data was collected and reviewed by FOs and then crosschecked by DTCs to verify diagnosis and to confirm notification status. Study data was entered in an Access database (Microsoft, Redmond, WA, USA) and NTP data in an Excel spreadsheet. After data cleaning and validation by double data entry of study data in Access database completeness of registration was explored by adding records from all three sources and duplicates were removed (inventory method). Data quality was improved by cross validation between data sources (91). Every fifth record on data file was crosschecked by a hard copy to ensure validity of data. Record linkage was performed using combination of first, father's and family names as unique identifiers for each case. If at least three names were found as an absolute match between non-NTP and NTP data, case was considered as notified. Completeness of NTP registers was assessed by comparing list of all patients identified by study with those recorded in NTP registers.

In paper III (Loss of patients with presumptive TB) the NTP research team conducted supervision to health facilities. To ensure proper implementation of the strategy the DTCs were involved to supervise the process. DOTS facilitators checked completeness and accuracy of the data by comparing the exit outpatient register with preliminary diagnosis of patients with the laboratory registers on weekly basis. Research monitoring team from NTP also cross-checked and verified missing patients with presumptive TB identified in list from comparison of two registers.

In paper IV (Initial loss to follow up), a search of registers in the entire district was undertaken to identify duplicate registration and was continued for 3 months (one calendar quarter) after end of study period to ensure that patients who were subsequently recorded were not missed. Close monitoring was also done to ensure data accuracy and completeness.

In Paper V (Active case finding in slums)in order to avoid duplication of cases, project-trained private providers were asked to maintain separate records for cases investigated and detected in chest camps and their clinic.

3.9 Sample Size

In the inventory study, all non-NTP facilities in 12 selected districts were mapped and all consenting providers were enrolled. Data on all patients with presumptive TB of cough more than 2 weeks who consulted public or private providers for their symptoms from January to March 2012 were collected. In Paper III (Loss of patients with presumptive TB), outpatient and laboratory registers were reviewed to collect data of patients with presumptive TB. Data of all lost patients with presumptive TB in the two study districts were collected by comparing both registers. In Paper IV (Initial loss to follow up), we enrolled all patients recorded in the laboratory registers in Rawalpindi district during 2009. Paper V (Active case finding in slums) was focused on a community based intervention through chest champs and involving private providers for identification of TB cases so calculation of sample size was not done.

3.10 Statistical Analysis

In Paper I (Inventory Study) data from partially overlapping registers of TB in community were analysed using capture-recapture methods (92), which examines the extent of overlap between sources in order to estimate the total number of unobserved cases. Capture-recapture methods involve cross-matching records from at least three incomplete data sources covering the same population to identify the number of cases common to paired lists. Then using information about overlapping and statistical methods we estimated the number of TB cases not identified in any of lists (57,58,93–98). Basic assumptions of capture-recapture analysis include: perfect record linkage; no migration/emigration/death (a "closed" population); cases are independent (99).

Final dataset consisted of matched records from NTP, non-NTP private and private laboratory; in addition to matched records between NTP and non-NTP public. Data from all sources were analysed using capture-recapture analysis to examine the extent of overlap between sources to estimate total number of unobserved cases. Log-linear models were applied to three or more data registers so that dependencies between sources could be accounted for via interaction terms. Denoting capture by each source as A, B and C and indexing these sources by i, j and k, respectively, expected counts E (n_{ijk}) are expressed as follows:

$$\text{Log E } (n_{ijk}) = \mu_0 + \mu_A x_A + \mu_B x_B + \mu_C x_C + \mu_{AB} x_{AB} + \mu_{AC} x_{AC} + \mu_{BC} x_{BC} + \mu_{ABC} x_{ABC}$$

Where x terms are indicator variables and μ terms are log risk ratios, e.g., x_{AB}corresponds to capture by both source A and B and μ_{AB} is an interaction term for these sources. Typically, 3-way interaction term μ_{ABC} is omitted so that estimation can proceed. $\mu_0$term corresponds to capture by none of the sources and therefore, its exponential $\exp(\mu_0)$ provides an estimate of number of unobserved cases. Total number of cases is then given by $N_{obs} + \exp(\mu_0)$, where N_{obs} is total observed TB cases. Further details and limitations of methods and assumptions are described elsewhere (56,100).

Eight standard models (including three possible 2-way interactions) and three non-standard models (including 3-way interaction at expense one of 2-way interactions) were applied and model with lowest Akaike Information Criteria (AIC) value was chosen with lower value indicating better models. This is a standard method for model selection in capture-recapture studies (56).These models also incorporated 2-source overlap between NTP and non-NTP public providers which we assumed to be independent. Estimates were therefore an average of 3-source model and the 2-source model based on model fits 2-source data AIC.

The selected model was then used to predict total number of TB cases in Pakistan by adjusting for sampling design. It allowed for proportion of observed cases to be estimated (observed/estimated total) denoted case ascertainment rate estimated proportion of notified cases is the number of TB cases after record linkage (NTP) divided by the estimated total (93). By applying the estimated proportion of NTP notifications to annual number of notified TB patients in all districts in 2011–2012, we obtained an estimate of total number of TB patients in Pakistan of 2012. All analyses were performed using Stata version 12 (Stata Corp, College Station, TX, USA).

In Paper II (Private investigation practices) secondary analysis of the inventory study's data set was performed. Frequency distributions were computed to describe the investigation, management and referral of patients with presumptive TB by private providers.

In Paper III (Loss of patients with presumptive TB), assessment of the effectiveness of intervention by comparing case detection in intervention and control districts, and also case detection before and after in intervention district was done. For comparison, contingency tables were computed and percentage change was calculated by assessing the difference between before and after intervention.

In Paper IV (Initial loss to follow up) frequency distributions were computed to describe data. Determinants of initial loss to follow up were age, gender, distance and

type of facilities. Contingency tables, chi-square test, odds ratios and their respective 95% confidence intervals (CIs) were calculated.

In Paper V (Active case finding in slums): Data were analysed using SPSS version 18 (IBM Corp, Armonk, NY, USA). Major determinants were age, sex, type of TB case, source of case detection and area. After data entry and cleaning, proportions were computed and group differences were analysed using chi-square test. For purpose of comparison, project areas were divided into inside and outside Karachi, and project case detection was compared with non-project areas.

3.11 Ethical Considerations

In Paper I (Inventory Study) the ethics approval was obtained from research ethic review committee of NTP. Informed consent was obtained from non-NTP providers but not from patients as it was only record review. Data collection tools were basically routine TB registers with minor modifications to collect relevant data.

In Paper III (Loss of patients with presumptive TB), Study was approved by research ethics review committee of NTP. The research involved only record review and no interaction between researcher and patient was done.

In Paper IV (Initial loss to follow up),Study was approved by Ethics Advisory Group of International Union against TB and Lung Disease (The Union), Paris, France and National Ethics approval was obtained.. It was based on record review of laboratory registers and treatment registers so individual patient consent was considered not to be required.

In Paper V (Active case finding in slums) , the study was a TB REACH funded project through Stop TB Partnership. Sponsor had no influence on study design or data collection. Project was approved by research ethics review committee, NTP. As study involved retrospective analysis of routine information from NTP project, individual patient consent was not required.

4. Results

4.1 Paper I: Estimating tuberculosis burden and case detection in Pakistan

In inventory study, a total of 8346 TB cases were identified in 12 districts between January to March 2012. Of these, 6061 (73%) were recorded in NTP TB register. Among all diagnosed cases during the study 2633 (32%) were diagnosed in non-NTP sector. A total of 348 (4%) patients were known to both NTP and non-NTP sector and 2285 (27%) were not notified to NTP. After adjusting for sampling design, proportion of cases notified to NTP was estimated at 32% (95% CI 17–49) and estimated case ascertainment was 45%. The estimated incidence in study area of 878 000 cases (95%CI 573 000–1 675 000) in a year and adjusting for population in Pakistan a rate of 497 (95% CI 324–948) per 100 000 population per year was obtained.

4.2 Paper II: Investigation of presumptive tuberculosis cases by private providers: lessons learnt from a survey in Pakistan

A total of 3048 patients with presumptive TB were identified by private providers from 12 districts of Pakistan from January to March 2012. Out of these patients 39.3% were referred for both sputum smear and CXR, 19.7% were referred only for sputum smear examination, 24% of cases were referred for CXR only, 0.5% of cases were referred for culture and 16.6% of cases were referred for other tests. Private providers gave treatment to 29.1% of these patients and referred remaining. Of whom 55% were referred to NTP diagnostic centres, 27.8% were non-NTP private laboratories (27.8%) and 15% to non-NTP public laboratories. Among referred cases, only 314 (26.4%) were registered with district TB centre (NTP). Among presumptive TB patients only 28.3% did not have TB: 23.4% had smear-positive pulmonary TB, 16.9% had smear-negative pulmonary TB, 4.5% had extra-pulmonary TB and 26.9 had unspecified pulmonary TB.

4.3 Paper III: Can the number of presumptive tuberculosis cases lost in general health services in Pakistan be reduced?

In this study, a simple strategy was tested whether marking patient names with presumptive TB can in the outpatient register help the clinicians to reduce the lost to follow-up . A total of 13183 patients with presumptive TB were recorded in outpatient registers from January to June 2013 before the intervention and of them, 1119 (8.5%) were not found in laboratory registers. Majority of presumptive TB cases were identified at primary health care level and more were lost here. After intervention (July to December 2013), 15564 TB presumptive cases were recorded in outpatient registers and lost patients with presumptive TB was 1073 (6.9%). Intervention significantly reduced the proportion of patients with presumptive TB lost from 8.5% to 6.9%. In "intervention districts" case notification increased from 1877 (quarters 1+2) to 2081 (quarters 3+4). In control districts case notification fell from 1293 (quarters 1+2) to 1213 (quarters 3+4). The change in case notification was significantly greater in the intervention than in the control districts (OR 1.2; 95% CI: 1.1-1.3).

4.4 Paper IV: Comprehensiveness of primary services in the care of infectious tuberculosis patients in Rawalpindi, Pakistan

A total of 16145 patients with presumptive TB were screened for TB and recorded in laboratory registers. Among them, 9711 were in tertiary care hospitals and 6434 were in RHCs. A total of 1698 patients (10% of registered patients with presumptive TB) were found to be smear-positive, more in RHCs (n =856, 13%) than in tertiary care hospitals (n =842, 9%, P <0.01). Among smear-positive patients in laboratory registers, 101 (6%) were not identified in treatment registers and this initial loss was statistically higher in tertiary care hospitals: 86 (10%) in tertiary care hospitals and 15 (2%) in RHCs). Larger initial loss to follow-up was associated with increasing age (P <0.01). Sex and distance from health facility were not statistically associated with initial loss to follow up. Proportion of missing smear-positive patients was lower in RHCs than in tertiary care hospitals.

4.5 Paper V: Success of active tuberculosis case detection among high-risk groups in urban slums in Pakistan

A project implemented two interventions for TB case detection in Pakistan: arranging chest camps to identify individuals to be examined for TB, and engaging general practitioners.

In chest camps, 165280 clients were screened and 13 481 (8.2%) were examined by sputum smear microscopy and among these 1707 (12.6%) were found to be sputum smear-positive. In addition to camps, 7747 individuals were referred from private providers for sputum smears examination in same areas and 1410 (18.2%) were sputum smear-positive. The yield of smear-positive cases in patients with presumptive TB identified from camps varied among districts from 9% to 14% but among the private providers more variation in yield was observed.

During pre-intervention period, a total of 10374 TB cases (all types) were notified to PTP; while in intervention period, reported TB cases significantly increased to 14140. Distribution of age and sex was same in both periods. Total number of cases reported increased steadily in each calendar quarter over project period in both Karachi and other areas.

5. DISCUSSION

This section describes methodological issues including strengths and limitations of the studies. It also discusses the major findings related to each paper.

5.1 Methodological issues

5.1.1 Study Design

In inventory study, in order to adopt a representative way to measure the burden of TB in Pakistan we used cross sectional designs as a recommended design to measure burden (101) . The data was collected from four clusters based on their notification rates and districts from each cluster were randomly selected. Capture-recapture study only investigates persons seeking care from various providers and those who do not seek help and suffer at home are not included. Such cases need a house to house prevalence survey to be accounted for. In inventory study, data quality was enhanced through prospective collection of data and record linkage from three separate sources was done .This method is inexpensive compared with other population-based sampling methods (102).

In Paper III (Loss of patients with presumptive TB), a cohort study was done to evaluate the effect of simple intervention in reduction of loss of patients with presumptive TB. The longitudinal nature of study design helped us to see the effects of intervention, it was possible to document the changes in outcome of interest (103,104).

In paper IV (Initial loss to follow up), a retrospective record review of routine NTP data was done to assess the loss to follow up after the diagnosis. however, quality of data and completeness of information are weakness associated with record reviews (105).

In Paper V (Active case finding in slums), Quasi experimental design was employed to assess increase in TB case notification in an intervention i.e. chest champs and involving private providers. A quasi-experimental study design is a type of evaluation which compares effect of a program in pre and post intervention period with no randomization (106).

5.1.2 Validity of studies

Results of any research always depend upon quality of data. However, data may be affected by study participants, instruments used, recall and biological variation. Epidemiological studies are always designed to minimize errors as much as possible and it aims to assess practical effects of any unavoidable error (107). The validity of study depends on design, conduct and analysis (103). With respect to population in which the conclusion is drawn, the term validity refers to two population groups, study population (internal validity) and general population (external validity).

5.1.2.1 Internal Validity

Internal validity refers to accuracy of measuring what study is designed to measure. It can be evaluated by role of chance (Random Sampling Error), presence or absence of selection bias, information bias, confounding and Hawthorne effect (103).

Chance refers to random error that occurs as a result of sampling variability. The role of chance is estimated by conducting the test of statistical significance and taking adequate sample size (107,108). To obtain a high degree of precision, the recommended sampling fraction is 50% in capture-recapture studies (99). Due to huge number of facilities in Pakistan and resource constraints, we selected 12 districts out of a total of 131 districts (9%). This is the reason for low degree of precision in Paper I (Inventory Study). Randomization technique in selection minimizes occurrences of outcomes by chance (109,110), but the effect of randomization is more limited when sample size is small, which also has an impact on the confidence limits.

Selection bias refers to systematic errors that arise in process of selecting study subjects and can be reduced by using a clearly defined eligibility criteria in design and conduct of a study (103,107,111).

All non-NTP facilities in the selected districts were mapped and visited in first phase of project and consenting providers were enrolled. To ensure completeness of data all type of health care providers were included in selected districts. In this process, some non-NTP providers may have been missed. Moreover all registered TB cases in national surveillance database were included in analysis and also all types of health care providers were included which exist in our health system i.e. non NTP private, non-NTP public, unregistered practitioners, traditional healers, hakims and homeopaths . However, there was no mechanism to include people who didn't have access to health care, those who were not under treatment and suffering at home for various reasons.

Seasonal variation of incidence and case notification is well known and may have an impact of measuring changes in case detection. In paper III (Loss of presumptive TB cases), the increase in case notification in the intervention districts could be caused by the regular seasonal variation, but this is less likely, as the control districts did not have the same increase. In paper V, the study went over 18 months and total number of cases reported in the districts increased steadily for each calendar quarter over the project period. Thus, seasonal variation had no direct effect on results.

Information bias is systematic error that refers to whether information is collected from study participants in the same way regardless of exposure status, presence of any measurement error or both (103,112).In inventory study, assumptions and limitations of capture-recapture analysis are described elsewhere. The validity of capture-recapture estimates depends on possible violations of underlying assumptions: unique identifier, perfect record-linkage, closed and homogeneous population (56,113–119). In our study, information on individual unique identifiers

(four names in Urdu) minimized violations of perfect record linkage. Visits of FOs every week improved completeness of registers. The study period lasted 3 months to minimize violation of closed population assumption by reducing population mobility. NTP registers were examined two quarters before and one quarter after study period to check and correct any misclassification of patients not diagnosed during study period or referred late for notification.

This approach has been used in studies to estimate TB in other resource-limited settings (58,93,96). As non-NTP public provider's data did not overlap with non-NTP private providers, this could not be used as a third source; non-NTP laboratories were therefore used as a third source and data from NTP, non-NTP private providers and non-NTP laboratories were used for final log linear analysis. This was preferred as it was less likely to be compromised by violation of assumption of independence as opposed to two linked registers which do not allow between-source dependence (56,100,120,121).

To minimize information bias, a pilot study was done in 2008 to assess feasibility of a capture-recapture study and data collection tool in our setting (90). Based on lessons learned from pilot study measures were taken to increase validity. For example, in the pilot study all health care providers were not included, only non-NTP registered private practitioners were enrolled which contributed to missing information; therefore only two data sources were used instead of three and log linear modeling could not be done (58,96). These lessons learned in pilot study were used in current study to improve validity, more health care providers were included and log linear modeling was done on four datasources. TB and laboratory registers in private sector were modified according to standard NTP guidelines. To ensure completeness and validity of data, national program officers (NPOs) and DTCs were involved to supervise FOs in data collection. Proper training was conducted on data collection tools. All non-NTP health facilities were visited weekly by FOs with NPOs and DTCs twice in a month to check records with instructions to collect missing names for proper record linkage and evaluate accuracy and notification status of TB cases. All non-registered non-NTP cases were contacted weekly by DTCs to verify

diagnoses as per NTP criteria. Data quality was improved by cross validation between data sources and data quality audit (91). Possible bias due to interdependencies between registers was adjusted by using log linear modelling via interaction terms from at least three linked registers (100,120–126). However there is a strong possibility of a 3-way interaction, unmeasured heterogeneity or both. The standard saturated model gave a good model fit but unreasonably high estimates of TB cases. We therefore selected a non-standard model that allowed for a 3-way interaction at expense of lower-order interaction between non-NTP private health facilities and private laboratories. We attempted to assess potential heterogeneity according to age and found that this did not affect our results; however, it is of course not possible to assess heterogeneity according to unmeasured covariates such as health care-seeking behavior. A relatively low overlap between registers led to wide CIs with consequent imprecision in estimated TB incidence.

Confounding occurs when a confounding variable are distributed unevenly and related to both exposure and outcome and can lead to either overestimation or underestimation of results. In Paper III (Loss of patients with presumptive TB) testing whether presumptive TB patients are taken better care of by marking names in OPD register may be confounded by close monitoring by DTC as this was not routine arrangement and would probably remind doctors and hence improve follow-up.

Hawthorn Effect refers to observer effect in which study participants improve their behavior in response to their awareness of being observed. In paper III (Loss of patients with presumptive TB), better outcome may be partly a result of strict monitoring by field supervisors and DTCs in intervention districts like a "Hawthorne" effect. Clinicians may become more attentive to TB by these frequent reminders and trace those lost to follow up.

5.1.2.2 External Validity

External validity refers to generalizability of research findings (103,127). For capture-recapture studies in order to obtain a high degree of precision, the

recommended sampling fraction is 50%. In inventory study, this was a challenge because of huge number of districts across the country and resource constraints. Our result from investigating 12 selected districts has wide CIs and in order to be representative and valid for rest of Pakistan's districts (which has a great variation of TB incidence rates) we selected clusters of districts based on case notification rates and randomly within each cluster. We think this contributes to making findings valid and useful for Pakistan.

In paper III (Loss of patients with presumptive TB) the strategy was based on improvement of routine practices without any new register and we think this can be implemented throughout the country.

The study described in Paper IV (Initial loss to follow up) was done in only one district with particularly high initial loss to follow-up and we think the lesson from this study can be used in similar settings like other large cities in Pakistan with large tertiary care hospitals. There is need to re-evaluate the strategy involving more major cities which may be different in socio demographic characteristics and TB control measures. The findings of Paper V (Active case finding in slums) are relevant and probably valid for other large city slums in Pakistan.

5.2 Discussion of major findings

5.2.1 Tuberculosis burden in Pakistan

In Paper I (Inventory study) we found that a substantial proportion of TB cases were identified in non-NTP public and private sectors but proportion notified was observed to be quite low only 32% . The estimated TB incidence rate (497/100000 population) was more than double official rate and observed under-reporting of detected cases was 27%, almost similar to studies with same design in Yemen (29%), Iraq (31%) and Egypt (28%) (57,58,96). Mandatory TB notification from private providers is not practised in Pakistan and anti- TB drugs are available over the counter (128). An estimated annual incidence of over 800000 cases is not unreasonable. This generated evidence that TB burden has been underestimated (129) and the country has

significant under-reporting also evident by the prevelance survey which demonstrated, the prevelance of 348 per 100,000 the estimated the patients daignotic rate of 41.5% for adults>15 years suggests that a high proportion of cases are missing in the community (130) . Moreover inventory study showed that many non-NTP providers refer to NTP laboratories for diagnosis . One obvious reason could be free diagnostic services at NTP laboratories. However, NTP registration process of diagnosed TB cases occurs at the time of treatment initiation and not from laboratory register. Ideally all confirmed TB cases referred from any source should be directly registered to NTP register after diagnosis at NTP laboratory.This may contribute to observed under-reporting and need to be addressed in strategies planned by NTP to minimize missing cases from all health care providers.

5.2.2 Private practitioners' investigations of patients with presumptive TB

In paper II (Private investigation practices), we found that 39.3% of Patients with presumptive TB were referred both for Sputum smear examination and CXR. This is encouraging, as another study from Sindh showed less use of laboratory although there was limited coverage (60) . Moreover, private providers referred majority (70.9%) of all patients with presumptive TB and treated only 29.1%, which needs to be improved by better coordination between private providers and laboratories. Although private providers rely on NTP diagnostic centers, 55% of referred cases were sent for diagnosis to NTP, after investigation from NTP results are sent back to doctor who requested for further follow-up and these referred cases were often not notified to NTP (131). Greater collaboration between private sector and NTP is needed for effective control of TB in country. Private providers in Pakistan do not always follow NTP guidelines for TB management, and motivation of providers to manage TB in clinics varies(46,132). Utilization of public sector and smear microscopy in current study shows there is potential for scaling up PPM approach across the country with proper training of private providers and informing laboratories as well as NTP staff about the prevailing routines in this regard (52).

5.2.3 Loss-to-follow-up of patients with presumptive TB

Paper III (Loss of patients with presumptive TB) addresses challenge of loss of patients with TB symptoms before diagnosis as observed by monitoring missions in the country (87,88) . Our study showed that simple intervention of marking patients with presumptive TB in outpatient register and comparing them with laboratory register on a weekly basis significantly reduced loss of TB symptomatic before diagnosis. Previous studies(133–135) mostly focused on loss-to-follow-up of TB cases after diagnosis and limited evidence is available on loss before diagnosis. A major proportion of TB symptomatic and lost ones were in primary/secondary level health facilities where most of these patients go first. This may be explained by a weak referral system for diagnosis from BHUs to higher levels, insufficient knowledge or perceived complicated procedure for diagnosis (133). This may be improved by better coordination between primary and tertiary level. The intervention reduced the proportion of lost patients by 4% and this reduction was significant at primary level but possible explanation of less reduction at tertiary level may be huge workload and over burden staff. In paper III (Loss of presumptive TB cases), the increase in case notification in the intervention districts could be caused by regular seasonal variation, but this is less likely, as the control districts did not have the same increase.

5.2.4. Initial loss of TB cases after diagnosis

The study provided evidence that more than one in 20 identified infectious TB patients was not registered on treatment. Proportion of cases initially lost to follow up was lower than reported in many other studies from around the world(63–65,133,136–138). Less loss to follow up in RHCs might be explained by better access to care in term of less distance from patient house and proper follow-up of patients. Moreover due to possible low workload at RHCs, health workers were able to give more time to counsel and support TB patients. The higher rate of initial loss to follow-up in tertiary care hospitals could be explained by higher workload, long

distance from patient to tertiary care facilities, cost of transport, inappropriate knowledge, attitude and practice of physicians (139,140). The results of current study demonstrate that there is a need to devise strategies to improve monitoring of registration, follow-up and care of smear-positive cases in tertiary care hospitals in Pakistan. Moreover, as these patients usually are not registered as they should be thus their treatment outcomes are not included as "lost to follow-up" and look better than they actually are(66).

5.2.5 Active case finding to increase TB notifications

Paper V (Active case finding in slums) provided evidence that district TB notification rate increased through community-based chest camps and engaging private providers of peri-urban slums who were not engaged by NTP. In current study, the yield of smear-positive cases among clients in camps suspected of having TB varied among districts from 9% to 14% but among private providers yield in each district varied much more. Other studies with different ACF strategies have found smear positive yields from 4% in South Africa to 13% in Ethiopia (77,141). Due to more sensitive and faster alternative to light microscope, LED-FM was used to screen sputum samples at chest camps which is recommended in low-income and high TB burden settings (142–144).

Many factors contribute to active case detection as a successful tool such as many people are not aware of TB symptoms by the time they develop symptoms and seek health care, their initial symptoms may have improved a little and they may go undetected. While through active case detection symptomatic patients can be diagnosed earlier. Community participation was improved by awareness campaign before chest camps. Motivation and training of local private providers was another key factor.

5.3 Strengths and limitations

Strengths: The strengths of inventory study were that it was implemented to estimate the under-reporting by all health care providers without using any intervention as part of their routine practices. The health care providers involved in the study provided a potential for the program for further strengthening linkages between program and health care providers who were otherwise not linked with the program. The Inventory study is a methodology which is less costly , less time consuming and more feasible as compared to TB prevalence surveys to estimate TB burden in the country (53). The study was of great benefit for the program and the findings were used to plan scale up of PPM approach as priority in the country.

Paper III (Loss of presumptive TB cases) focused on testing a simple strategy to minimize loss-to-follow-up of potential TB symptomatic before diagnosis. It reflects the reality in the health system in Pakistan and utilized a simple field intervention which can be easily replicated in the country without any additional cost. Moreover, the exact number of cases resulting from the intervention is unknown as no such record was maintained.

Paper IV (Initial loss to follow up) was done within the program settings as part of routine monitoring to address the challenge of loss to follow up of TB cases after diagnosis.A major strength of this study is inclusion of all health facilities in the district linked with NTP including tertiary care hospitals we believe that it may be representative of the situation in the rest of the country.

Paper V (Active case finding in slums) has several strengths. It included a large number of participants and a big province of Pakistan with many peri-urban slums and it was implemented as NTP project. It also focused on issues of high priority in the NTP which was enhancing case detection in neglected and untouched slums population. As NTP project the study had opportunity to collect the data and share the information and results within NTP and involving key stakeholders, hence ensured impact of the results and incorporation into policy and Practice.

Limitations: The Inventory study was based on routine data and it is difficult to ensure accuracy and completeness of data in routine practice. For capture-recapture studies in order to obtain a high degree of precision for incidence estimation, the recommended sampling fraction is 50% while in Pakistan it was not possible. This was one the main limitation in inventory study, because of huge number of districts across the country and resource constraint involved for the implementation at such wide scale. Moreover, those who were asymptomatic or without access to health care providers were not included in the study and they may have contributed to heterogeneity.

In paper III (Loss of presumptive TB cases), seasonal impact of changes could influence the results, but we think seasonal changes were fairly similar in intervention and control districts. The weekly visits as well as supervisory visits in intervention districts may have made clinicians more aware of the lost patients with presumptive TB in implementation districts, and trace those lost to follow up. This study was done in only two districts due to financial constraints so it was taken as a pilot study.

Paper IV (Initial loss to follow up) was limited by the fact that it was confined to one district and used routinely recorded data thus accuracy and completeness of data could not be ensured.

Paper V (Active case finding in slums) was a project evaluation after the project was over so information collected has all the weaknesses of record review of routine data Incentives were provided to private providers and health workers involved in the intervention. Therefore cost-effectiveness and the time investment from the local health department need to be evaluated for sustainability

5.4 Implications for Policy

Operational research done within context of country's national disease control programmes may enhance programme effectiveness and generate evidence for better

policy and planning. There was a need to investigate the challenges of undiagnosed/ undetected TB cases and test strategies to identify and minimize missing TB cases through operational research in Pakistan. The research was conducted within NTP setup using established NTP system with advantage to move fast to help influence policy and practice (145). In recent past, disease control was linked with various research initiatives in country (146) and considered as a way for good policy change and improvement in practices (147). NTP Pakistan has encouraged work done for this project and taken up results of all studies in future policy planning. Examples are results of paper I, II and V that were incorporated in National Strategic Plan vision 2020 (44) and in concept note for 2015-2017 for Global Fund Grant recently approved .

Involvement of all health care providers can significantly increase TB Case notifications and finding of paper I (Inventory study) was taken into account while planning a scale up of PPM approach in country from 2015 onwards. Likewise the evidence from paper II (Private investigation practices) is of great value for the program that we need to devise strategies to register those cases referred to NTP for diagnosis and are not registered and to enhance Private providers coverage for reporting to NTP. The timely evidence generated from Paper III (Loss of patients with Presumptive TB) helps the current ongoing Review of the Program from May 5th to May 12th 2015 ,to evaluate the strategy and recommend for better Presumptive TB management across the country. The lessons learned from paper V (Active case finding in slums) for active case finding are being taken up to replicate same strategy by one of principal recipient of global fund in Pakistan i.e. Mercy Corps. The results of paper IV are already taken up in plans to scale up tertiary care hospital coverage across the country and to improve hospital DOTS linkages.

6. Conclusion and Recommendations

6.1 Conclusions

Based on the findings in this thesis we reached the following conclusions.

1. The proportion of existing TB cases notified to Pakistan's NTP is quite low and estimates of Pakistan's annual incidence rate may be much higher than WHO estimates.
2. There is significant under-reporting from all heath care providers. A weak surveillance system could be one reason for the observed under-reporting.
3. Many private providers are treating TB cases without notifying them to NTP, although they rely on NTP laboratories for diagnosis.
4. Simple comparison of outpatient and laboratory registers on routine basis and tracing the lost TB symptomatics can reduce loss-to-follow up of patients with presumptive TB.
5. Follow-up and care of smear-positive cases in many tertiary care hospitals in Pakistan is poor.
6. Engaging private providers in community based chest camps and linking the private providers to register and notify can increase notification of TB cases.

6.2 Recommendations

Based on our findings, we suggest the following recommendations

1. The evidence generated from TB Inventory study using capture-recapture analysis for estimation of TB burden and Under-reporting clearly provide a roadmap for NTP Pakistan to scale up private-public-mix approach as a priority to enhance TB case detection and to minimize under-reporting...

2. Over the counter sale of TB drugs should be discouraged and consider banning TB drug outside NTP.The program should supply Anti TB drugs to all care providers dealing with TB in order to minimize TB case under-reporting as well as misuse and development of drug resistance.
3. Private providers should be engaged and linked to the NTP with proper training and motivation.
4. The presumptive TB case management should be strengthened by better program monitoring and involvement of DOTS facilitators to trace verified cases in the Laboratory registers who are not recorded in the TB treatment registers.
5. The program should strengthen Hospital DOTS linkage to improve TB control in Tertiary care hospitals, and to make effective collaboration between tertiary and primary care hospitals. A concept of TB focal person at each hospital may be very helpful so that patients are not missed from registration at tertiary care level (148).
6. Program should adopt innovative strategies like ACF through chest camps and engaging private providers in order to enhance TB case notifications in the country and to reach the unreached areas such as peri-urban slums

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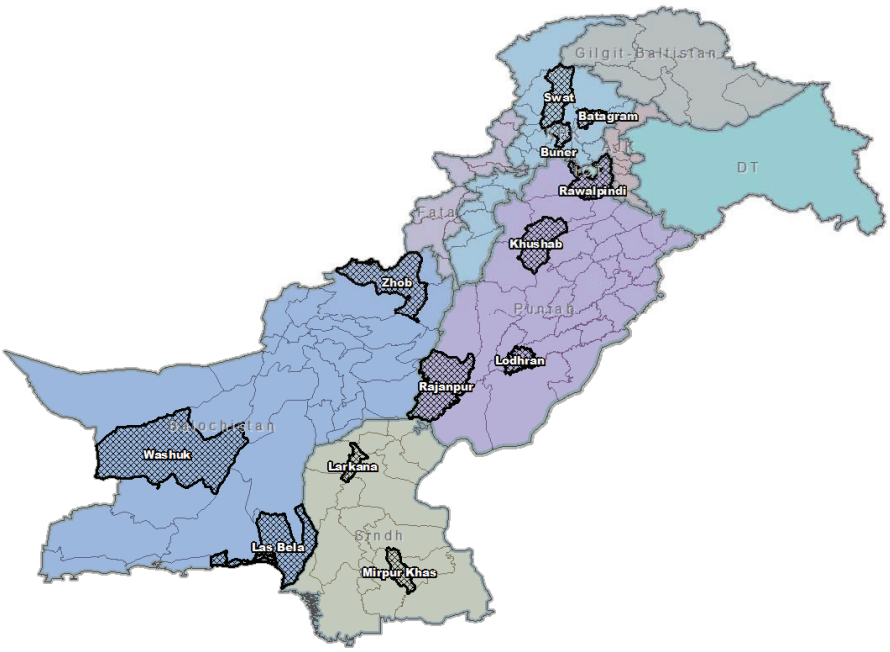
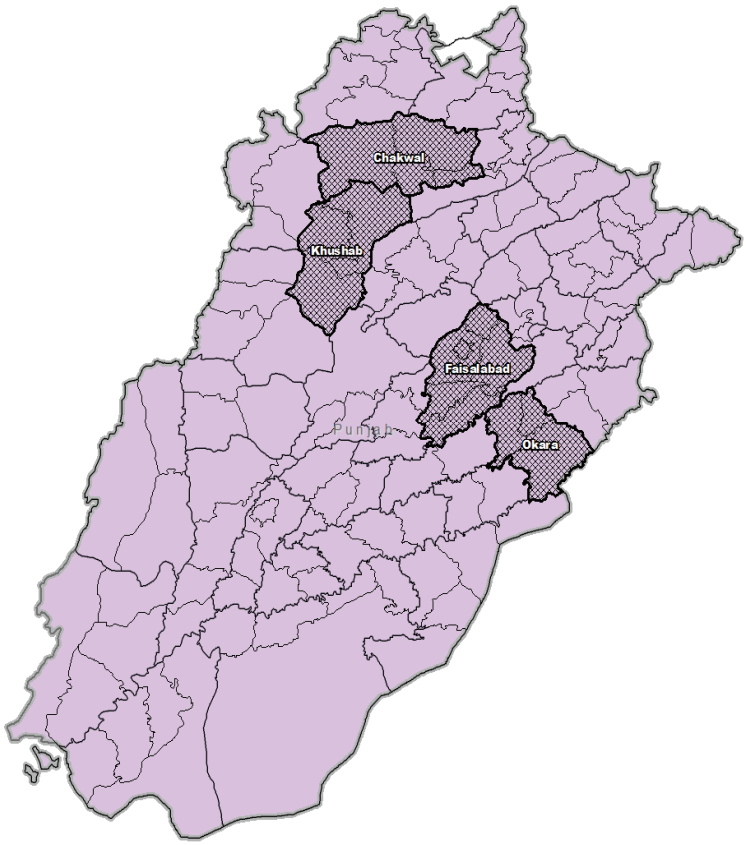
7. Annexes

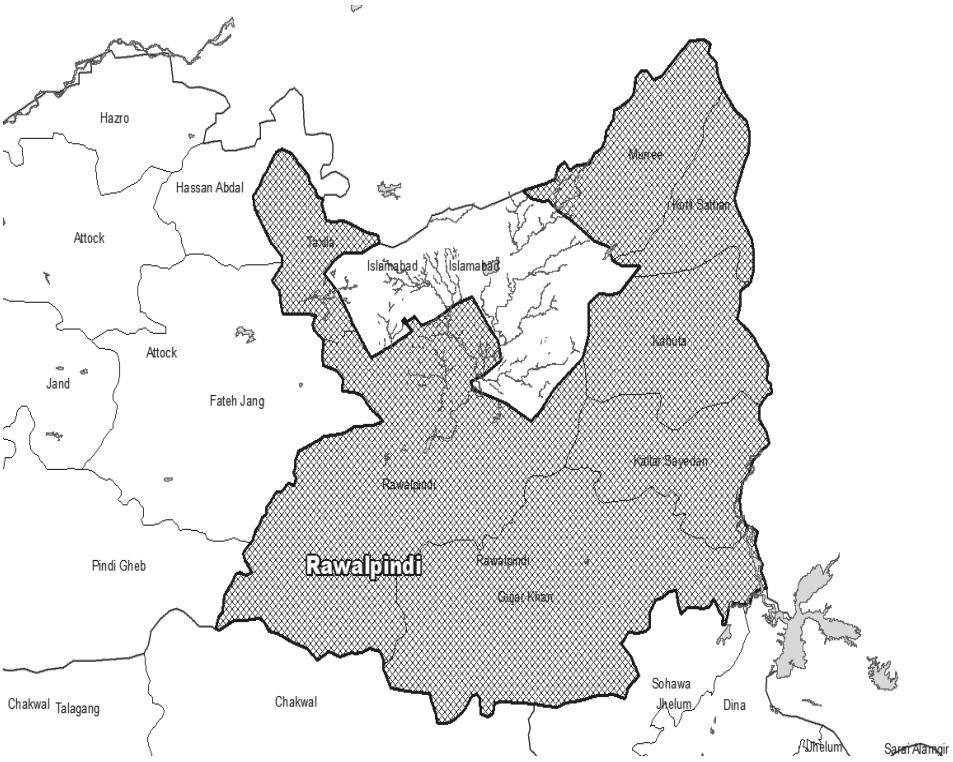
I: Map of Pakistan with the 12 districts across the country selected for paper I (Inventory study) & II (Private investigation practices)



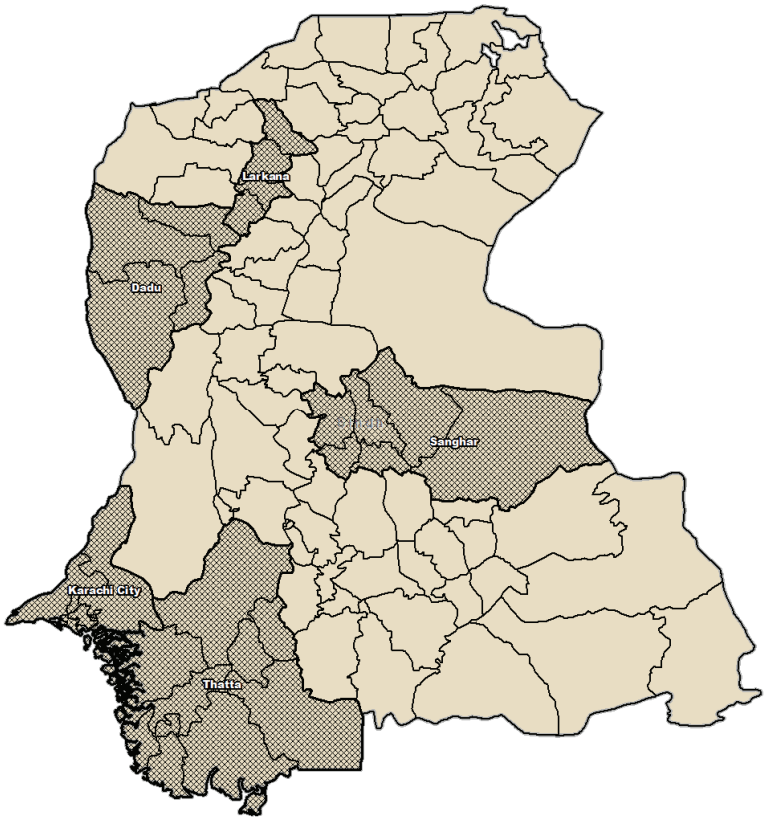
II: Map of Punjab province in Pakistan with intervention and control districts for paper III (Loss of presumptive TB cases)



III: Map of Rawalpindi district in Pakistan for paper IV (Initial loss to follow up)



IV: Map of selected districts in Sindh province in Pakistan for paper V (Active case finding in slums)



V: Data collection forms for Paper I (Inventory study)

Modified Register of TB Suspects and suspected Extra-pulmonary TB patients

Province_____ District_____ Facility Type_____Name of Provider_____ DTC name_____

Name of facility _____ Speciality_____Date of data collection_____ DTC signature_____

Serial No.	Date	Name of TB Suspect (pulmonary or extra-pulmonary)				Age (years)	Gender (M/F)	Complete Address (and telephone, mobile)	Nationality	ID Number	Requested investigations (from the same facility or through referral) 1=sputum smear examination 2-X-ray 3-both (1+2) 4-culture 5=others	Action taken 1=referred 2=diagnosed and referred for treatment 3=treated 4=None	Place of referral (1)	Reason of referral (2)	Provisional diagnosis made by the non-NTP 1=ss+ PTB 2=ss- PTB 3=PTB(unspecified) 4=EP 5=Not TB	*To be completed at the district/NTP*		
		First	Father's Husbandz name for married female	Grandfather's Husband: Grand father name in married female	Fourth name											Final Diagnosis 1=ss+ PTB 2=ss- PTB 3-PTB (unspecified) 4=EP 5=Not TB	Notification status at the TBMU register (NTP) Y=Yes; N=No	Date of initiation of Anti-TB treatment at the NTP (record date)

Definitions and codes

Facility Type:

Public:
- 1Public hospitals
- 2University hospitals (governmental)
- Parastatal
- Ministry of Interior (prisons)
- Ministry of Defense

Private
- Private hospitals
- Private teaching hospitals (private universities)
- Private clinics
- Private polyclinics
- NGOs
- Charity Based
- Others

Speciality:
-General Practitioners (GP)
-Chest physicians
-Internal Medicine specialists
-Others

Gender: M=male; F=female
Nationality: N=national; NN=non-national

Place of referral (1):
[1] District TB centre (NTP)
[2] public lab
[3] private lab
[4] other provider
[5] others, specify

Reason of referral (2):
[1] confirming diagnosis
[2] treatment
[3] NA (in case of treatment)

Modified Laboratory Register of TB Suspects and suspected Extra-pulmonary TB patients

Province_____District_____ Lab specialty_____Lab name _____ DTC name_____DTC signature_____
Date of data collection_____

Lab. serial No.	Date specimen received	Name				Age (years)	Gender (M/F)	Nationality (N/NN)	ID Number	Complete address (all patients) and Phone, mobile)	Referred by(1)	Type of reffering facility	Results of sputum smear microscopy z			Other laboratory investigations (Y/N)	*To be completed at the district/NTP*		
		First	Father' s Husbands name for married female	Grandfather' s Husbands Grand father name in married female	Fourth name								1	2	3		Final Diagnosis 1=s+ PTB 2=s- PTB 3-PTB (unspecified) 4=EP 5=Not TB	Notification status at the TBMU register (NTF) Y=Yes; N=No	Date of initiation of Anti-TB treatment at the NTP (record date)

Definitions and codes

Laboratory:
-private
-public

Referred by (1):
[1] self
[2] community: treatment supporter, etc.
[3] public provider
[4] private provider
[5] traditional healer, Informal practitioner
[6] drug store/pharmacies
[7] others

Gender: M=male; F=female
Nationality: N=national; NN=non-national

Results of sputum smear microscopy (Z):
(NEG): 0 AFB/100 fields;
(1-9 bac) exact number if 1 to 9 AFB/100 fields;
(+): 10-99 AFB/100 fields;
(++): 1-10 AFB/ field;
(+++): > 10 AFB/ field
Typ

Lab speciality
1] Microbiology
2]Pathology
3]General
4]other

Type of referring facility
Public:
- Public hospitals
- University hospitals (governmental)
- Parastatal
- Ministry of Interior (prisons)
- Ministry of Defense

Private
- Private hospitals
- Private teaching hospitals (private universities)
- Private clinics
- Private polyclinics
- NGOs
- Charity Based
- Others

Annex VI: Study instrument for paper III (Loss of presumptive TB cases)

LIST OF MISSING PRESUMPTIVE TB CASES

Sr .No	Name	Father/Husband Name	OPD Reg No	Gender	Age	Address	District	Treatment Center	Distance from Health facility

● ***The DOTS facilitator will compare the OPD register with Lab register on weekly basis and will make a list of missing suspect.***

Annex VII: Study instrument for paper IV (Initial loss to follow up)

LIST OF IDENTIFIED SUSPECTS

Sr .No	Name	Father/Husband Name	Gender	Age	Address	District	Lab Name	Lab Sr #	Diagnosis

Annex VIII:Ethics Approval for Study Protocol from Research Ethic Review Committee,NTP

Government of Pakistan, National Health

NATIONAL TB CONTROL PROGRAM

27th January, 2012

Dr Razia Fatima,
Research Coordinator,
National TB Control Program,
Islamabad.

Re: Ethical review of the PhD study protocol titled "Assessing the burden of Missing TB cases in Pakistan"

Dear Dr Razia Fatima,

Thank you for sending your PhD study protocol "Assessing the burden of Missing TB cases in Pakistan" for ethical review. The committee reviewed it in today's meeting and didn't find any serious ethical issue in the proposal as all of the studies will be based on record review of OPD, laboratory, treatment registers and retrospective record review of TB REACH project data so individual patient consent was considered not to be required. We hereby, approve the PhD study protocol for further process

Sincerely,

Dr Ejaz Qadeer,
National Manager/ Chairperson
Research Ethic Review Committee,
National TB Control Program, Pakistan

Annex IX: Additional **Ethics Approval for paper IV (Initial loss to follow up)**

International Union Against Tuberculosis and Lung Disease

Promoting lung health in low- and middle-income countries

Ethics Advisory Group Date: 3rd September 2010

To:

Razia Kaniz Fatima, National TB Control Program Pakistan

Title of research project:

Is Initial Default of smear-positive patients more common in tertiary care hospitals as compared to peripheral health facilities in Pakistan?

STUDY SITE(S)

Rawalpindi district : all peripheral diagnostic centers (14) and tertiary care hospitals (3)

I

Investigators:

Razia Fatima

Dr Noor Ahmed Baloch , Manager National Tuberculosis control Program

Dr Ejaz Qadeer , Deputy Director Technical National Tuberculosis Control Program

Dr Amal Bassil World Health Organisation

EAG number : 28/10

Thank you for your application to the Ethics Advisory Group of the Union. Your study has our formal approval.

We trust that your study proceeds well and that it will be productive.
With best wishes,

M.E. EDGINTON

Prof. Mary Edginton

Chairperson

Please forward a copy of the Local ethics committee approval to eag@theunion when this is available.

Union Internationale Contre la Tuberculose et les Maladies Respiratoires
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Annex X: Obituary of AmalBassilli (Co-Supervisor)

Public Health Action

International Union Against Tuberculosis and Lung Disease
Health solutions for the poor

VOL 4 NO 4 PUBLISHED 21 DECEMBER 2014

OBITUARY

Amal Bassilli, 1961–2014

Asma El Sony,[1,2] Donald A. Enarson[3]

http://dx.doi.org/10.5588/pha.14.0104

Amal Fawzi Bassilli, MD, MPH, DrPH, Assistant Professor of Medical Research and Medical Officer of the World Health Organization (WHO), died in August 2014, aged 53. Her death is a great loss to the international community working in the fight against tuberculosis (TB) and other non-communicable diseases (NCDs). Amal played an influential role in TB prevention and control, devoting herself to TB elimination and the Millennium Development Goals.

Dr Bassilli is internationally known through her research, teaching activities and her role in prevention and control of TB in the Middle East Region, and especially in resource-limited settings. As a Surveillance officer, STB/WHO/EMRO Focal point (2011–2014), Amal assisted several countries in planning and conducting population-based methods to directly measure TB incidence at national level and generating robust TB surveillance data to ascertain trends in disease burden and to assess the performance of TB control programmes. Amal's expertise in prevalence surveys was significant and is a reflection of how knowledge transfer is central to the Stop TB slogan to which she devoted her life.

Amal played an immense role in generating evidence through promoting capture-recapture methods to measure the TB burden at national level, and was instrumental in building the skills and capacities of consultants on monitoring and evaluation and the practical elements of surveillance through technical training courses.

As part of her mandate as coordinator of the Special Programme for Research and Training in Tropical Diseases (TDR) in the WHO Eastern Mediterranean Regional Office, Dr Bassilli contributed to strengthening research skills and research as a conceptual and technical component embedded within all disease prevention and control efforts. Dr Bassilli supported innovative research, evaluated interventions in real life settings, and supported the increase in access to interventions of TB prevention and control. Her work has had significant impact, particularly in exploring barriers to DOTS implementation and expansion at both community and health system levels.

Dr Bassilli contributed to the management of drug-resistant TB; her systematic review was a breakthrough, improving the quality of available evidence supporting the WHO recommendation that patients be treated using mainly ambulatory care, conditional on infection control measures in the home and clinic, the clinical condition of the patient, availability of treatment support to facilitate adherence to treatment, and provisions for backup facility to manage patients in need of in-patient care.

As an Associate Editor for *Public Health Action*, Amal contributed to disseminating new knowledge on health systems and health services for vulnerable groups, with a priority on tuberculosis, lung health, NCDs and general health services issues.

Dr Bassilli's belief that knowledge and skills in TB should spill over to other aspects of care was prominent, and she supported the novel utilisation of the TB model for other lung health conditions, where she provided technical support in the replication of the model to asthma and pneumonia in children aged under 5 years in first referral levels in the Middle East region.

Amal's work was comprehensive, tackling public health issues such as influenza, cardiovascular diseases as well as other NCDs. Her reputation and published work will continue to inspire generations in the battle against public health issues and in paving the way towards comprehensive human development.

Amal is survived by her husband, Professor Nashaat Lufti, and two sons, Shady and Rami.

AFFILIATIONS
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2 Past President, International Union Against Tuberculosis and Lung Disease, Paris, France
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PHA 2014; 4(4): 282

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e-ISSN 2220-8372
Editor-in-Chief: Dennis Maher, MD, Switzerland
Contact: pha@theunion.org
PHA website: http://www.theunion.org/index.php/en/journals/pha
Article submission: http://mc.manuscriptcentral.com/pha